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ATENT COOPERATION TR TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

NASH, David Allan.
Haseltine Lake & Co.
Imperial House
15-19 Kingsway
London WC2B 6UD
ROYAUME-UNI

Date of mailing (day/month/year)
20 September 2001 (20.09.01)

Applicant's or agent's file reference
2475/002631

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/05735

International filing date (day/month/year)
21 June 2000 (21.06.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
GOLDSCHEID, Bettina
BASF Aktiengesellschaft
D-67056 Ludwigshafen
Germany

State of Nationality:
State of Residence:
Telephone No.: 0621/60-78916
Facsimile No.: 0621/60-21183
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
NASH, David Allan.
Haseltine Lake & Co.
Imperial House
15-19 Kingsway
London WC2B 6UD
United Kingdom

State of Nationality:
State of Residence:
Telephone No.: 44 117 910 3200
Facsimile No.: 44 117 910 3201
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
David LOPEZ-RAMIREZ

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

NASH, David Allan.
Haseltine Lake & Co.
Imperial House
15-19 Kingsway
London WC2B 6UD
ROYAUME-UNI

Date of mailing (day/month/year)
29 octobre 2001 (29.10.01)

Applicant's or agent's file reference
2475/002631

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/05735

International filing date (day/month/year)
21 juin 2000 (21.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
KNOLL AKTIENGESELLSCHAFT
D-67061 Ludwigshafen
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
KNOLL GMBH
D-67061 Ludwigshafen
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Gabriele BAEHR
Telephone No.: (41-22) 338.83.38

EP/01-9921

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 February 2001 (14.02.01)	
International application No. PCT/EP00/05735	**Applicant's or agent's file reference** 2475/002631
International filing date (day/month/year) 21 June 2000 (21.06.00)	**Priority date** (day/month/year) 05 July 1999 (05.07.99)
Applicant LUSCOMBE, Graham, Paul et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   15 December 2000 (15.12.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. E. Stoffel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

ATENT COOPERATION TR TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and ~~Administrative Instructions, Section 422~~)

To:

COMPUTER

- 6 NOV 2001

NOTED

NASH, David Allan.
Haseltine Lake & Co.
Imperial House
15-19 Kingsway
London WC2B 6UD
ROYAUME-UNI

Date of mailing (day/month/year) 29 October 2001 (29.10.01)	
Applicant's or agent's file reference 2475/002631	IMPORTANT NOTIFICATION
International application No. PCT/EP00/05735	International filing date (day/month/year) 21 June 2000 (21.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
KNOLL AKTIENGESELLSCHAFT D-67061 Ludwigshafen Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
KNOLL GMBH D-67061 Ludwigshafen Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Gabriele BAEHR
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) ~~338.83.38~~

Form PCT/IB/306 (March 1994)

004407042

PATENT COOPERATION TRE.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
2475/002631		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/05735	21/06/2000	05/07/1999
Applicant		
KNOLL AKTIENGESELLSCHAFT		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   BICYCLIC AROMATIC COMPOUNDS FOR TREATING DRUG ADDICTION

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-11,14-16,20-23 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to those compounds mentioned specifically by name in the description and claims, and , based on those compounds, a generalisation of their structural formulae to encompass compounds having the following structural features: A and B are -O-.

Claims searched completely: 12,13,14-19
Claims searched incompletely: 1-11,20-23

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

International Application No
PCT/EP 00/05735

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/517 A61K31/357 A61K31/497 A61K31/453 A61K31/4709
A61K31/4545 A61K31/4433 A61K31/506 A61P25/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 62902 A (KNOLL AG ;BIRCH ALAN MARTIN (GB); WISHART NEIL (GB)) 9 December 1999 (1999-12-09) abstract page 1, line 1 - line 13 page 6, line 17 - line 32; claims 1-10; examples	1-4, 7-11,14, 16,20-23
X	WO 95 07274 A (BOOTS CO PLC ;HEAL DAVID JOHN (GB); KERRIGAN FRANK (GB); MARTIN KE) 16 March 1995 (1995-03-16) cited in the application abstract page 1, line 1 - line 17 page 12, line 18 - line 31; claims 1-20; examples	1-23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2001	06/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 03071 A (KNOLL AG ;BIRCH ALAN MARTIN (GB); HEAL DAVID JOHN (GB); KERRIGAN F) 30 January 1997 (1997-01-30) abstract page 1, line 1 - line 13 page 15, line 4 - line 33; claims; examples ---	1-23
A	WO 98 40386 A (KNOLL AG ;BIRCH ALAN MARTIN (GB); BRADLEY PAUL ANTHONY (GB)) 17 September 1998 (1998-09-17) abstract page 1, line 1 - line 13 page 12, line 14 -page 13, line 17; claims 1-19; examples ---	1-23
A	WO 97 43279 A (BOSMANS JEAN PAUL R M ;LOMMEN GUY ROSALIA EUGENE VAN (BE); LOVE CH) 20 November 1997 (1997-11-20) abstract page 9, line 12 - line 25; claims; table 3 ---	1-23
A	GB 1 237 158 A (INSTITUT TOXIKOLOGH MINISTERSTVA ZDRAVOOKHRANENIA) 30 June 1971 (1971-06-30) the whole document -----	1-23

2

Information on patent family members

International Application No
PCT/EP 00/05735

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9962902 A	09-12-1999	AU 4369599 A	20-12-1999
WO 9507274 A	16-03-1995	AT 191214 T	15-04-2000
		AU 689802 B	09-04-1998
		AU 7692894 A	27-03-1995
		BG 100388 A	31-07-1996
		BR 9407413 A	12-11-1996
		CA 2170056 A	16-03-1995
		CN 1133043 A,B	09-10-1996
		CZ 9600614 A	11-09-1996
		DE 69423767 D	04-05-2000
		DE 69423767 T	20-07-2000
		DK 717739 T	10-07-2000
		EP 0717739 A	26-06-1996
		ES 2144528 T	16-06-2000
		FI 961016 A	05-03-1996
		GR 3033575 T	29-09-2000
		HU 75875 A	28-05-1997
		IL 110844 A	28-10-1999
		JP 9502431 T	11-03-1997
		NO 960888 A	05-03-1996
		NZ 273581 A	27-05-1998
		PL 313347 A	24-06-1996
		PT 717739 T	31-07-2000
		RU 2136680 C	10-09-1999
		SI 9420058 A	31-12-1996
		SK 27196 A	01-10-1996
		US 5767116 A	16-06-1998
		ZA 9406798 A	06-04-1995
WO 9703071 A	30-01-1997	AU 708890 B	12-08-1999
		AU 6517296 A	10-02-1997
		BG 62771 B	31-07-2000
		BG 102145 A	30-11-1998
		BR 9609506 A	01-06-1999
		CA 2223472 A	30-01-1997
		CN 1190967 A	19-08-1998
		CZ 9703884 A	17-06-1998
		EP 0839145 A	06-05-1998
		HR 960348 A	30-04-1998
		HU 9901485 A	28-07-2000
		JP 11508599 T	27-07-1999
		NO 980129 A	12-01-1998
		NZ 313164 A	29-07-1999
		PL 324529 A	08-06-1998
		SK 2498 A	09-09-1998
		US 5935973 A	10-08-1999
WO 9840386 A	17-09-1998	AU 6721598 A	29-09-1998
		EP 0966470 A	29-12-1999
WO 9743279 A	20-11-1997	AU 708344 B	05-08-1999
		AU 2956197 A	05-12-1997
		CN 1218466 A	02-06-1999
		CZ 9803627 A	17-02-1999
		EP 0912552 A	06-05-1999
		HU 9903445 A	28-05-2000
		JP 2000512623 T	26-09-2000

...information on patent family members

International Application No
PCT/EP 00/05735

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9743279 A		NO 985228 A	11-01-1999
		NZ 332308 A	30-08-1999
		PL 329850 A	12-04-1999
		US 6159982 A	12-12-2000
		ZA 9704050 A	09-11-1998
GB 1237158 A	30-06-1971	NONE	

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
BASF AKTIENGESELLSCHAFT
Attn. GOLDSCHEID, Bettina
D-67056 Ludwigshafen
GERMANY

Patente, Marken u. Lizenzen
12. FEB. 2001

	Date of mailing *(day/month/year)* 06/02/2001
Applicant's or agent's file reference 2475/002631	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP 00/05735	International filing date *(day/month/year)* 21/06/2000

Applicant

KNOLL AKTIENGESELLSCHAFT

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Joannes Vergoosen

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
~~2475/002631~~		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 05735	21/06/2000	05/07/1999

Applicant

KNOLL AKTIENGESELLSCHAFT

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   BICYCLIC AROMATIC COMPOUNDS FOR TREATING DRUG ADDICTION

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

International Application No
PCT/EP 00/05735

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/517 A61K31/357 A61K31/497 A61K31/453 A61K31/4709
A61K31/4545 A61K31/4433 A61K31/506 A61P25/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 62902 A (KNOLL AG ;BIRCH ALAN MARTIN (GB); WISHART NEIL (GB)) 9 December 1999 (1999-12-09) abstract page 1, line 1 - line 13 page 6, line 17 - line 32; claims 1-10; examples	1-4, 7-11,14, 16,20-23
X	WO 95 07274 A (BOOTS CO PLC ;HEAL DAVID JOHN (GB); KERRIGAN FRANK (GB); MARTIN KE) 16 March 1995 (1995-03-16) cited in the application abstract page 1, line 1 - line 17 page 12, line 18 - line 31; claims 1-20; examples	1-23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2001	06/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/EP 00/05735

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 03071 A (KNOLL AG ;BIRCH ALAN MARTIN (GB); HEAL DAVID JOHN (GB); KERRIGAN F) 30 January 1997 (1997-01-30) abstract page 1, line 1 - line 13 page 15, line 4 - line 33; claims; examples	1-23
A	WO 98 40386 A (KNOLL AG ;BIRCH ALAN MARTIN (GB); BRADLEY PAUL ANTHONY (GB)) 17 September 1998 (1998-09-17) abstract page 1, line 1 - line 13 page 12, line 14 -page 13, line 17; claims 1-19; examples	1-23
A	WO 97 43279 A (BOSMANS JEAN PAUL R M ;LOMMEN GUY ROSALIA EUGENE VAN (BE); LOVE CH) 20 November 1997 (1997-11-20) abstract page 9, line 12 - line 25; claims; table 3	1-23
A	GB 1 237 158 A (INSTITUT TOXIKOLOGH MINISTERSTVA ZDRAVOOKHRANENIA) 30 June 1971 (1971-06-30) the whole document	1-23

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-11,14-16,20-23 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to those compounds mentioned specifically by name in the description and claims, and , based on those compounds, a generalisation of their structural formulae to encompass compounds having the following structural features: A and B are -O-.

Claims searched completely: 12,13,14-19
Claims searched incompletely: 1-11,20-23

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/05735

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 2-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

IN RNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/05735

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9962902 A	09-12-1999	AU 4369599 A	20-12-1999
WO 9507274 A	16-03-1995	AT 191214 T	15-04-2000
		AU 689802 B	09-04-1998
		AU 7692894 A	27-03-1995
		BG 100388 A	31-07-1996
		BR 9407413 A	12-11-1996
		CA 2170056 A	16-03-1995
		CN 1133043 A,B	09-10-1996
		CZ 9600614 A	11-09-1996
		DE 69423767 D	04-05-2000
		DE 69423767 T	20-07-2000
		DK 717739 T	10-07-2000
		EP 0717739 A	26-06-1996
		ES 2144528 T	16-06-2000
		FI 961016 A	05-03-1996
		GR 3033575 T	29-09-2000
		HU 75875 A	28-05-1997
		IL 110844 A	28-10-1999
		JP 9502431 T	11-03-1997
		NO 960888 A	05-03-1996
		NZ 273581 A	27-05-1998
		PL 313347 A	24-06-1996
		PT 717739 T	31-07-2000
		RU 2136680 C	10-09-1999
		SI 9420058 A	31-12-1996
		SK 27196 A	01-10-1996
		US 5767116 A	16-06-1998
		ZA 9406798 A	06-04-1995
WO 9703071 A	30-01-1997	AU 708890 B	12-08-1999
		AU 6517296 A	10-02-1997
		BG 62771 B	31-07-2000
		BG 102145 A	30-11-1998
		BR 9609506 A	01-06-1999
		CA 2223472 A	30-01-1997
		CN 1190967 A	19-08-1998
		CZ 9703884 A	17-06-1998
		EP 0839145 A	06-05-1998
		HR 960348 A	30-04-1998
		HU 9901485 A	28-07-2000
		JP 11508599 T	27-07-1999
		NO 980129 A	12-01-1998
		NZ 313164 A	29-07-1999
		PL 324529 A	08-06-1998
		SK 2498 A	09-09-1998
		US 5935973 A	10-08-1999
WO 9840386 A	17-09-1998	AU 6721598 A	29-09-1998
		EP 0966470 A	29-12-1999
WO 9743279 A	20-11-1997	AU 708344 B	05-08-1999
		AU 2956197 A	05-12-1997
		CN 1218466 A	02-06-1999
		CZ 9803627 A	17-02-1999
		EP 0912552 A	06-05-1999
		HU 9903445 A	28-05-2000
		JP 2000512623 T	26-09-2000

IP RNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/05735

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9743279 A		NO 985228 A	11-01-1999
		NZ 332308 A	30-08-1999
		PL 329850 A	12-04-1999
		US 6159982 A	12-12-2000
		ZA 9704050 A	09-11-1998
GB 1237158 A	30-06-1971	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2475/002631		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05735	21/06/2000	05/07/1999

International Patent Classification (IPC) or national classification and IPC
C07D405/00

Applicant
KNOLL AKTIENGESELLSCHAFT et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/12/2000	02.11.2001

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer
Büttner, U
Telephone No. +49 89 2399 7841

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05735

I. **Basis of the report**

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, pages:

1-19 as originally filed

Claims, No.:

1-23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-23.

because:

☒ the said international application, or the said claims Nos. 2-23 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-11, 20-23 (all partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	22
	No:	Claims	1-21, 23
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1

No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 2-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The Applicant is aware that the search has been carried out for those parts of the application which are clear/or supported within the meaning of Art. 6 PCT and /or disclosed within the meaning of Art. 5 PCT.
Consequently, the examination can only be carried out for those parts of the application (claims 12-19) which have been completely searched (see search report; sheet PCT/ISA/210).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 95 07274 A
D2: WO 97 03071 A
D3: WO 98 40386 A

(N)

Claim 1 (partially)

Compounds falling under the scope of claim 1 and their use as a medicament is known from D1 (whole document, especially p.7-9), D2 (whole document, especially p. 7-12) and D3 (whole document, especially p. 8). Hence the subject matter of claim 1 is not novel.

Claims 2-11, 20, 21, 23 (all partially), 12-19

The use of compounds as defined in claims 12 and 13 (and thus falling into the scope of claims 2-11) for the treatment of drug addiction is taught in D1 (p.1, l.10; claims 12 ,15, 19, 20). Hence the subject matter of claims 2-11, 20, 21, 23 (all partially), 12-19 is not novel.

Claim 22 (Partially)

The specific use for the claimed compounds where the addictive substance is one of the substances as defined in claim 22 is not disclosed in D1. Therefore the subject matter of claim 22, for those parts that have been searched, is considered to be novel.

(IS)

Claim 22 (Partially)

The problem to be solved by the present invention may be regarded as to provide a medicament for reducing cravings to food or addictive substances, especially substances defined in claim 22.

From the examples (p. 12-19) however it is not clear which specific compounds have been tested actually and thus for which compounds the problem has been solved.

Furthermore there would be no justification to extrapolate from one specific test compound to all compounds embraced by claim 22.

Thus the subject matter of claim 22 does not solve the problem over the whole of its breadth.

(IA)

The requirements of industrial applicability are fulfilled for claim 1.

Claims 2-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item VIII

Certain observations on the international application

Formula III as mentioned on page 11, l. 18 and page 12 l. 6 can not be found.

Claims 2-13 are not clear, since they depend on claim 1, which is another category of claim (Article 6 PCT).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/02391 A2

(51) International Patent Classification[7]: C07D 405/00

(21) International Application Number: PCT/EP00/05735

(22) International Filing Date: 21 June 2000 (21.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9915616.8 5 July 1999 (05.07.1999) GB

(71) Applicant *(for all designated States except US)*: KNOLL AKTIENGESELLSCHAFT [DE/DE]; D-67061 Ludwigshafen (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LUSCOMBE, Graham, Paul [GB/GB]; R3 Pennyfoot Street, Nottingham NG1 1GF (GB). NEEDHAM, Patricia, Lesley [GB/GB]; R3 Pennyfoot Street, Nottingham NG1 1GF (GB).

(74) Agent: GOLDSCHEID, Bettina; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

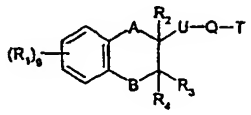
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

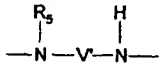
Published:
— *Without international search report and to be republished upon receipt of that report.*

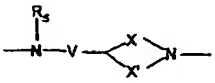
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

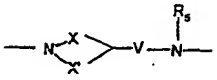
2475/02631
020908

(54) Title: THERAPEUTIC AGENTS


(I)


(IIb)


(IIa)


(IIc)

(57) Abstract: Compounds of formula (I) and pharmaceutically acceptable salts thereof in which A is methylene or -O-; B is methylene or -O-; and g is 0, 1, 2, 3 or 4; R_1 represents, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkylthio, hydroxy, acyloxy, hydroxymethyl, cyano, alkanoyl, alkoxycarbonyl, optionally N-substituted carbamoyl, carbamoylmethyl, sulphamoyl or sulphamoylmethyl, an amino group optionally substituted by one or two alkyl groups, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring; R_2 is H, alkyl or alkoxy; R_3 and R_4, which are the same or different, are H, or alkyl; U is an alkylene chain optionally substituted by one or more alkyl; Q represents a divalent group of formula (IIa, IIb or IIc) in which V is a bond or an alkylene chain optionally substituted by one or more alkyl; V' is an alkylene chain optionally substituted by one or more alkyl; X is a bond or an alkylene chain and X' is an alkylene chain, provided that the total number of carbon atoms in X and X' amounts to 3 or 4; R_5 is H, or alkyl; and T represents an optionally substituted aromatic group which optionally contains one or more N atoms, provided that T is not 2-pyrimidinyl when A is -O-; have utility in reducing cravings to food or an addictive substance.

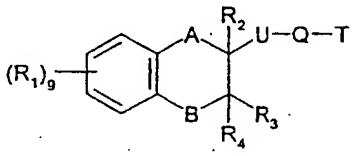
WO 01/02391 A2

Therapeutic Agents

The present invention relates to the use of compounds for reducing cravings for food or an addictive substance in mammals particularly human beings.

WO95/07274 discloses the use of a compounds of formula I as shown below as novel compounds useful for treating depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, eating disorders, anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, prostatic hypertrophy, or spasticity.

The present invention provides compounds of formula I



including pharmaceutically acceptable salts thereof in which

A is methylene or -O-;

B is methylene or -O-;

g is 0, 1, 2, 3 or 4;

R_1 represents a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) hydroxymethyl, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl

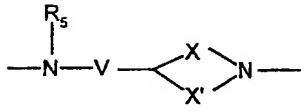
group containing 2 to 6 carbon atoms, k) a carbamoyl group or carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring, the substituents represented by R_1 being the same or different when g is 2, 3 or 4;

R_2 is H, an alkyl group containing 1 to 3 carbon atoms, or an alkoxy group containing 1 to 3 carbon atoms;

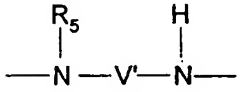
R_3 and R_4, which are the same or different, are H, or an alkyl group containing 1 to 3 carbon atoms;

U is an alkylene chain containing 1 to 3 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

Q represents a divalent group of formula IIa, IIb or IIc



IIa



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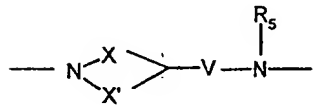


IIc

in which V is a bond or an alkylene chain containing 1 to 3 carbon atoms optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

V' is an alkylene chain containing 2 to 6 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

X is an alkylene chain containing 0 to 2 carbon atoms and X' is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in X and X' amounts to 3 or 4; R_5 is H or an alkyl group containing 1 to 3 carbon atoms; and

T represents an aromatic group optionally containing one or more N atoms and optionally substituted by one or more substituents selected from halo, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, or a polyhalogenated alkyl group, for example trifluoromethyl, or T represents benzo[b]furanyl or benzodioxanyl with the proviso that T is not 2-pyrimidinyl when A is -O- for use in reducing cravings to food or an addictive substance.

In preferred compounds of formula I, A is -O-.

In preferred compounds of formula I, B is -O-.

In more preferred compounds of formula I both A and B are -O-.

In preferred compounds of formula I, g is 0, 1 or 2.

In preferred compounds of formula I, R_1 represents halo (for example fluoro, chloro, or bromo), an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring. In more preferred compounds of formula I, R_1 represents methoxy, fluoro, chloro, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring.

In preferred compounds of formula I, R_2 is H or an alkyl group containing 1 to 3 carbon atoms. In more preferred compounds of formula I, R_2 is H.

In preferred compounds of formula I, R_3 and R_4, which are the same or different, are H or methyl. In more preferred compounds of formulaI, R_3 and R_4 are both H.

In preferred compounds of formula I, U is methylene.

In preferred compounds of formula I in which Q is a group of formula IIa or IIc, V is methylene or ethylene.

In preferred compounds of formula I, in which Q is a group of formula IIb, V' is an alkylene chain containing 2 to 4 carbon atoms.

In preferred compounds of formula I, R_5 is H or methyl. In more preferred compounds of formula I, R_5 is H.

In preferred compounds of formula I, T is pyridyl, pyrimidinyl, pyrazinyl, phenyl, benzo[b]furanyl, 1,4-benzodioxanyl or quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo (eg fluoro, chloro or bromo). In more preferred compounds of formula I, T is 2-pyridyl, 2-pyrimidinyl, 2-pyrazinyl, phenyl, 2,3-dihydrobenzo[b]furan-7-yl, 1,4-benzodioxan-5-yl or 4-quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo (eg fluoro, chloro or bromo).

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. Compounds of formula I and their salts may exist in the form of solvates (for example hydrates).

Compounds of formula I contain one or more chiral centres, and exist in different optically active forms. When compounds of formula I contain one chiral centre, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers. The enantiomers may be

resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallisation; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of formula I contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to this skilled in the art, for example chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof. Certain compounds of formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Specific compounds of formula I are:-

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrazin-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-chloropyrid-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(quinazolin-4-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine;

N-(8-Methoxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-N'-[3-(trifluoromethyl)-2-pyridyl]ethanediamine;

N-(8-Methoxy-1,2,3,4-tetrahydronaphth-2-ylmethyl)-1-[1-pyrimidin-2-yl)piperid-4-yl]methylamine;

7-{N-[1-(Pyrimidin-2-yl)piperid-4-ylmethyl]aminomethyl}-5,6,7,8-tetrahydronaphth-1-ol;

N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-ylmethyl)-1-[1-(pyrimidin-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-(1-phenylpiperid-4-yl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(1,4-benzodioxan-5-yl)piperid-4-yl]methylamine;

1-[1-(1,4-Benzodioxan-2-ylmethyl)piperid-4-yl]-N-(2-methoxyphenyl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(4-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-Methoxy-1,4-benzodioxan-2-ylmethyl)-N'-(2-methoxyphenyl)-1,3-propanediamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-methoxyphenyl)piperid-4-yl]methylamine;

N-(6,7-Dichloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-chlorophenyl)piperid-4-yl]methylamine;

N-(5-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

1-[1-(2-methoxyphenyl)piperid-4-yl]-N-(naphtho[1,2-b]dioxan-2-ylmethyl)methylamine;

1-[1-(2,3-Dihydrobenzo[b]furan-7-yl)piperid-4-yl]-N-(8-methoxy-1,4-benzodioxan-2-ylmethyl)methylamine;

N-(6-chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(7-chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-hydroxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

Specific enantiomeric forms of compounds of formula I include:

(S)-(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(R)-(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride;

(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride.

The present invention also includes pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or a salt thereof together with a pharmaceutically acceptable diluent or carrier.

As used hereinafter, the term "active compound" denotes a compound of formula I or a salt thereof. In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethyl- cellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, for example paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as a suspension or solution in a pharmaceutically acceptable oil of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes any compound of the invention but particularly any compound which is the final product of one of the preceding Examples.

a) Capsules

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing a unit dose of part of a unit dose of active compound.

b) Tablets

Tablets are prepared from the following ingredients.

	Parts by weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinyl-pyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate

and the rest of the starch. The mixture is then compressed in a tabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

Enteric coated tablets

Tablets are prepared by the method described in (b) above. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or III may be used to treat drug misuse or other addictive disorders. Whilst the precise amount of active compound administered in such treatment will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history, and always lies within the sound discretion of the administering physician, the amount of active compound administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg given in single or divided doses at one or more times during the day.

In another aspect the present invention provides a method of treating drug misuse or other addictive disorders which comprises the administration of a therapeutically effective amount of a compound of formula I to a patient in need thereof.

The present invention provides a method of reducing cravings to food or an addictive substance in a mammal comprising administering an effective amount of a compound of formula I to a mammal in need thereof.

Suitably the addictive substance is cocaine, amphetamine, nicotine, opiates, tobacco or alcohol. The addictive substance may also be MDMA (ecstasy), a cannabinoid, LSD, MDA or PCP. .The term opiates includes heroin and morphine.

In yet another aspect, the present invention provides the use of a compound of formula I or III in the manufacture of a medicament for use in the treatment ofdrug misuse or other addictive disorders.

Conditions which may be advantageously treated with the compounds of the present invention include disorders arising from drug misuse including drug withdrawal symptoms, aiding in the cessation of smoking, aiding in the prevention of relapse after cessation of drug use and similar use in the treatment of other addictive disorders such as compulsive gambling, compulsive shopping disorder and compulsive sexual disorder.

In another aspect the present invention provides a method of treating addictive-drug-induced psychoses comprising administering a therapeutically effective amount of a compound of formula I to a mammal, particularly a human being, in need thereof.

Addictive drugs which may cause psychoses include benzodiazepines, cannabinoids, LSD, MDMA, MDA, PCP, opiates including heroin and morphine, amphetamine, cocaine and alcohol.

The pharmacological activity of the compounds of the present invention may be demonstrated by one or more of the following tests.

STUDY 1 METHODS

Subjects: The subjects are four male rhesus monkeys *(Macaca mulatta)*, weighing 5.7-8.1 kg and maintained on a diet of 3-4 monkey biscuits and one piece of fresh fruit per day. During the week, all food is delivered after the experimental session, whereas at weekends, food is delivered between 9 a.m. and noon. Water is

freely available at all times. The monkeys are housed in a humidity and temperature controlled room with a 12 h light-dark cycle (lights on from 7 a.m. to 7 p.m.).

Apparatus: Each monkey is housed individually in a well-ventilated, stainless steel chamber (56 x 71 x 69 cm) which includes an operant panel (28 x 28 cm) mounted on the front wall. Three response keys are arranged in a horizontal row 3.2 cm from the top of the operant panel. Each key can be transilluminated by red or green stimulus lights (Superbright LEDs). An externally mounted pellet dispenser delivers 1 g fruit-flavoured food pellets to a food receptacle beneath the operant response panel. A computer, located in a separate room, controls the operant panels and data collection.

Discrimination Training: Discrimination training is conducted 5 days per week during daily sessions composed of multiple cycles. Each cycle consists of a 15 min time-out period followed by a 5 min response period. During the time-out, all stimulus lights are off, and responding has no scheduled consequences. During the response period, the right and left response keys are transilluminated red or green, and monkeys can earn up to 10 food pellets by responding under a FR 30 schedule of food presentation. For one monkey, the left key is illuminated green and the right key is illuminated red, the colours of the response-keys are reversed for the other three monkeys. The centre key is not illuminated at any time and responding on it has no scheduled consequences. If all available food pellets are delivered before the end of the 5 min response period, the stimulus lights are turned off and responding has no scheduled consequences for the remainder of the 5 min period.

On training days, monkeys are given either saline or 0.40 mg/kg cocaine, i.m., 10 min before the response period. Following the administration of saline, responding on only the green key (the saline-appropriate key) produces food, whereas following administration of 0.40 mg/kg cocaine, only responding on the red key (the drug-appropriate key) produces food. Responses on the inappropriate key reset the FR requirement on the appropriate key. Sessions consist of 1 to 5 cycles and, if cocaine is administered, this occurs only during the last cycle. Thus, training days consist of 0 to 5 saline cycles followed by 0 or 1 cocaine cycle.

During each response period, 3 dependent variables are determined:

1) Percent injection-appropriate responding prior to delivery of the first reinforcer.

2) Percent injection-appropriate responding for the entire response period

3) Response Rate.

Monkeys meeting the following criteria during the training day immediately proceeding the test day and in at least 6 of 7 consecutive training sessions before this are used for discrimination testing:

1) the percent injection-appropriate responding prior to delivery of the first reinforcer is ≥ 80% for all cycles;

2) the percent injection-appropriate responding for the entire cycle is ≥ 90% for all cycles;

3) Response rates during saline training cycles are >0.5 responses per second.

If responding did not meet criterion levels of discrimination performance, then training is continued until criterion levels of performance are obtained for at least two consecutive days.

Discrimination Testing: Test sessions are identical to training sessions except that responding on either key produces food, and the test compound is administered using a Pretreatment Protocol. In this protocol, a cumulative dose-effect curve for cocaine (0.013-1.3 mg/kg) is determined either alone or following pretreatment with the test compound, which is administered 20 min before the first dose of cocaine.

Mean data from saline and drug cycles during the training day immediately proceeding the initial test day serve as the control data for the subsequent test day.

Data Analysis: The Percent Cocaine-Appropriate Responding and the Response Rate are plotted as a function of the dose of cocaine (log scale). Where possible, the ED_{50} value for cocaine is determined by drawing a line between the points above and below 50% cocaine-appropriate responding, and then using linear regression to interpolate the dose that would produce 50% cocaine-appropriate responding. ED_{50} values for cocaine administered alone and following pretreatment with the test compound are then compared.

Drugs: Cocaine hydrochloride is dissolved in sterile saline. The test compound is dissolved in 1% lactic acid in distilled water.

RESULTS

Control mean saline-appropriate responding = 99.8% (± 0.2) and 100% appropriate responding are obtained during cocaine cycles.

ED_{50} values for cocaine are calculated. Administration of cocaine alone produces a dose-dependent increase in cocaine-appropriate responding in all four monkeys. Complete substitution is obtained at the training dose of cocaine (0.4 mg/kg) in all monkeys, and a higher dose of 1.3 mg/kg usually decreases response rates. Pretreatment with 0.01 mg/kg of the test compound produces a rightward shift in the cocaine dose-effect curve and a 3-fold increase in the cocaine ED_{50} value in monkey 2, but it has no effect on the cocaine discrimination dose-effect curve in the other three monkeys. A higher dose of 0.032 mg/kg of the test compound produces rightward shifts in the cocaine dose-effect curves in all four monkeys. The test compound (0.01 and 0.032 mg/kg) also eliminated responding during the first one to three cycles of the cumulative cocaine dose-effect curve determination (i.e. in combination with 0.013 and 0.04 mg/kg cocaine). However, monkeys responded after administration of higher cocaine doses, thereby permitting evaluation of the effects on cocaine discrimination. Interestingly, response rates following administration of the highest dose of cocaine (1.3 mg/kg) are often higher following

test compound pretreatment than for cocaine alone, suggesting that the test compound attenuated the rate-decreasing effects of high cocaine doses.

These studies can establish that the test compound antagonises the discriminative stimulus effects and possibly also the rate decreasing effects of cocaine at doses that also produce effects on response rates by comparing ED_{50} values (mg/kg) for cocaine administered either alone or after pretreatment with test compound.

STUDY 2 METHODS

Subjects: The subjects are four male rhesus monkeys *(Macaca mulatta)*. Each monkey is maintained on a diet of 3 monkey biscuits and one piece of fresh fruit per day in addition to fruit-flavoured pellets delivered during operant sessions (see below). Water is freely available at all times. The monkeys are housed in a humidity and temperature controlled room with a 12 hr light-dark cycle (lights on from 7 a.m. to 7 p.m.).

Monkeys are surgically implanted with double-lumen silicone rubber catheters (inside diameter 0.7 mm, outside diameter 2.0 mm) to facilitate concurrent delivery of cocaine and treatment compounds. Catheters are implanted in the jugular or femoral vein and exteriorized in the midscapular region. All surgical procedures are performed under aseptic conditions. Monkeys are sedated with ketamine (5 mg/kg, s.c.), and anaesthesia is induced with sodium thiopental (10 mg/kg, i.v). Monkeys receive 0.05 mg/kg atropine, to reduce salivation. Following insertion of a tracheal tube, anaesthesia is maintained with isoflurane (1-1.5% in oxygen). After surgery, monkeys are administered aspirin or acetaminophen (80-160 mg/day; p.o.) for 3 days and Procaine Penicillin 0 (300,000 units/day, i.m.) every day for 5 days. The i.v. catheter is protected by a tether system consisting of a custom-fitted nylon vest connected to a flexible stainless steel cable and fluid swivel (Lomir Biomedical; Malone, NY), which permits the monkeys to move freely. Catheter patency is periodically evaluated by i.v. administration of the short-acting barbiturate methohexital (3 mg/kg i.v.) or ketamine (2-3 mg/kg i.v.). The catheter is considered

patent if i.v. administration of methohexital or ketamine produces loss of muscle tone within 10 seconds after its administration.

Apparatus: Each monkey is housed individually in a well-ventilated stainless steel chamber (64 x 64 x 79 cm which includes an operant panel (28 x 28 cm) mounted on the front wall. Three response keys (6.4 x 6.4 cm) are arranged in a horizontal row 3.2 cm from the top of the operant panel. Each key can be transilluminated by red or green stimulus lights (Superbright LEDs). An externally mounted pellet dispenser delivers 1 g fruit-flavoured food pellets to a food receptacle beneath the operant response panel. Two syringe pumps are mounted above each cage for delivery of saline or drug solutions through the intravenous catheters. Operant panels and data collection are controlled by a computer through a MED-PC interface.

Training: As shown in the diagram below, food and i.v. drug or saline injections are available during three alternating components: a 5 min food component, a 100-min drug component, and a second 5 min food component. Both food and i.v. injections are available under a FR 30 schedule of reinforcement. During the two food components, the response key is transilluminated red. During the drug component, the response key is transilluminated green. Following the delivery of each food pellet or drug injection, there is a 10 sec timeout period, during which the stimulus light illuminating the centre response key is turned off and responding has no scheduled consequences. The food and drug components are separated by 5-min timeout periods when the response key is dark, and responding has no scheduled consequences. The entire food/drug/food session lasts 120 min.

In addition to the food/drug/food session described above, monkeys are also given the opportunity to self-administer additional food pellets during supplementary food sessions. During these sessions, food is available under a FR30/Timeout 10 sec schedule, and a maximum of 25 pellets per session can be earned. These food sessions provide additional enrichment opportunities for the monkeys and behavioural information relevant for the evaluation of prolonged treatment drug effects.

During training, the solution available for self-administration during the drug component is alternated between 0.032 mg/kg/inj cocaine (the maintenance dose of cocaine) and saline. Each period of cocaine or saline availability usually lasts from 3 to 10 days. Monkeys are trained until they met the following criteria for stable cocaine self-administration: 1) three consecutive days during which the response rate during the drug component of each session differs by no more than 20% from the mean drug component response rate and there is no upward or downward trend; and 2) rapid saline extinction as indicated by a decrease in drug component response rates on the first day of saline substitution.

Evaluation of Test Compound: The effects of the test compound (0.0032-0.10 mg/kg) on cocaine self-administration and food-maintained behaviour are evaluated using the standard pretreatment test procedure. In this procedure, the test compound is administered i.m. 20-min prior to a test session during which a test unit dose of cocaine is available during the drug component. Two series of studies are described here. In the first, the unit dose of cocaine is 0.0032 mg/kg/inj (at or near the peak of each monkey's cocaine self-administration dose-effect curve) and the effects of pretreatment with each dose of test compound are determined in single sessions for all monkeys. In the second series of studies, the effects of pretreatment with each of two doses of the test compound (0.003 and 0.01 mg/kg) on the entire cocaine dose-effect function are determined. In these studies, the dose of cocaine is systematically varied for single test sessions after pretreatment with each dose of the test compound. Both the dose of cocaine and the pretreatment dose of the test compound are varied across test sessions in an irregular order among monkeys.

At the conclusion of each pretreatment test in either series of studies, training conditions (availability of saline or the maintenance dose of cocaine) are reinstated. Test sessions generally are conducted on Tuesdays and Fridays, and either saline or the maintenance dose of cocaine is available during training sessions for the remainder of the week. On occasion, another dose of cocaine is substituted for the maintenance dose to insure that the position of the cocaine dose-effect function in individual monkeys is stable. In addition, test days are occasionally omitted to allow several days of saline substitution.

Data Analysis: The dependent variables are the response rates during each food and drug component. The response rate is calculated as [total # responses (component duration - S timeouts)]. Control response rates for each food and drug component during availability of each unit dose of cocaine are defined as the response rate obtained when that unit dose of cocaine is available and no pretreatment is administered. The ED_{50} value for the test compound during each food or drug component is defined as the dose of the test compound that decreases rates of cocaine or food self-administration to 50% of control response rates. The ED_{50} values are determined where possible by linear regression from the linear portion of the test compound dose-effect curve.

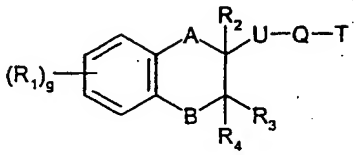
For subsequent studies, in which the unit dose of cocaine is varied and the pretreatment dose of the test compound is held constant, response rates are graphed as a function of the unit dose of cocaine. Control cocaine dose-effect curves are determined in the absence of pretreatment and are visually compared to cocaine dose-effect curves determined following pretreatment with the test compound.

Drugs: Cocaine hydrochloride is dissolved in saline. A stock solution of 10 mg/ml of the test compound is prepared using a vehicle of 1% lactic acid in distilled water, and dilutions are made with distilled water. Aseptic precautions are taken in every phase of cocaine solution preparation and dispensing. Cocaine solutions are filter-sterilised using a 0.22 micron Millipore Filter and stored in sterile, pyrogen-free vials. Sterility of the entire fluid path for drug solutions is maintained throughout the study. Each unit dose of cocaine is delivered i.v. in an injection volume of 0.1 ml. Doses of the test compound are delivered i.m. in a volume of 0.2-3.0 ml.

These studies can establish that treatment with the test compound diminishes cocaine self-administration and food-maintained behaviour.

Claims

1. Compounds of formula I



including pharmaceutically acceptable salts thereof in which

A is methylene or -O-;

B is methylene or -O-;

g is 0, 1, 2, 3 or 4;

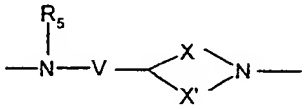
R_1 represents a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) hydroxymethyl, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring, the substituents represented by R_1 being the same or different when g is 2, 3 or 4;

R_2 is H, an alkyl group containing 1 to 3 carbon atoms, or an alkoxy group containing 1 to 3 carbon atoms;

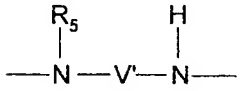
R_3 and R_4, which are the same or different, are H, or an alkyl group containing 1 to 3 carbon atoms;

U is an alkylene chain containing 1 to 3 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

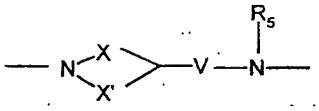
Q represents a divalent group of formula IIa, IIb or IIc



IIa



IIb



IIc

in which V is a bond or an alkylene chain containing 1 to 3 carbon atoms optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

V′ is an alkylene chain containing 2 to 6 carbon atoms, optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms;

X is an alkylene chain containing 0 to 2 carbon atoms and X′ is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in X and X′ amounts to 3 or 4;

R_5 is H or an alkyl group containing 1 to 3 carbon atoms; and

T represents an aromatic group optionally containing one or more N atoms and optionally substituted by one or more substituents selected from halo, an alkyl

group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, or a polyhalogenated alkyl group, or T represents benzo[b]furanyl or benzodioxanyl with the proviso that T is not 2-pyrimidinyl when A is –O-; for use in reducing cravings to food or an addictive substance.

2. The use of compounds of formula I as claimed in claim 1 wherein A is -O-.

3. The use of compounds of formula I as claimed in any preceding claim wherein B is -O-.

4. The use of compounds of formula I as claimed in any preceding claim wherein g is 0, 1 or 2.

5. The use of compounds of formula I as claimed in any preceding claim wherein R_1 represents halo, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring.

6. The use of compounds of formula I as claimed in any preceding claim wherein R_1 represents methoxy, fluoro, chloro, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring.

7. The use of compounds of formula I as claimed in any preceding claim wherein R_2 is H or an alkyl group containing 1 to 3 carbon atoms.

8. The use of compounds of formula I as claimed in any preceding claim wherein R_3 and R_4, which are the same or different, are H or methyl.

9. The use of compounds of formula I as claimed in any preceding claim wherein T is pyridyl, pyrimidinyl, pyrazinyl, phenyl, benzofuryl, 1,4-benzodioxanyl or quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

10. The use of compounds of formula I as claimed in any preceding claim wherein T is 2-pyridyl, 2-pyrimidinyl, 2-pyrazinyl, phenyl, 2,3-dihydrobenzo[b]furan-7-

yl, 1,4-benzodioxan-5-yl or 4-quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

~~11. The use of compounds of formula I as claimed in any preceding claim~~ wherein R_5 is H or methyl.

12. The use of compounds of formula I as claimed in claim 1 which are:

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrazin-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-chloropyrid-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(quinazolin-4-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine;

N-(8-Methoxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-N'-[3-(trifluoromethyl)-2-pyridyl]ethanediamine;

N-(8-Methoxy-1,2,3,4-tetrahydronaphth-2-ylmethyl)-1-[1-pyrimidin-2-yl)piperid-4-yl]methylamine;

7-{N-[1-(Pyrimidin-2-yl)piperid-4-ylmethyl]aminomethyl}-5,6,7,8-tetrahydronaphth-1-ol;

N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-ylmethyl)-1-[1-(pyrimidin-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-(1-phenylpiperid-4-yl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(1,4-benzodioxan-5-yl)piperid-4-yl]methylamine;

1-[1-(1,4-Benzodioxan-2-ylmethyl)piperid-4-yl]-N-(2-methoxyphenyl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(4-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-Methoxy-1,4-benzodioxan-2-ylmethyl)-N'-(2-methoxyphenyl)-1,3-propanediamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-methoxyphenyl)piperid-4-yl]methylamine;

N-(6,7-Dichloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-chlorophenyl)piperid-4-yl]methylamine;

N-(5-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

1-[1-(2-methoxyphenyl)piperid-4-yl]-N-(naphtho[1,2-b]dioxan-2-ylmethyl)methylamine;

1-[1-(2,3-Dihydrobenzo[b]furan-7-yl)piperid-4-yl]-N-(8-methoxy-1,4-benzodioxan-2-ylmethyl)methylamine;

N-(6-Chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(7-Chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-hydroxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

13. The use of compounds of formula I as claimed in claim 12 which are:-

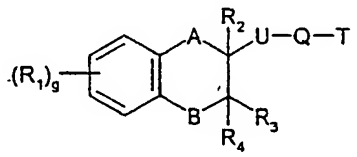
(S)-(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(R)-(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride;

(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride.

14) The use of compounds of formula I



and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers, in which

A is -O-;

B is -O-;

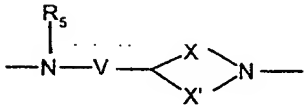
g is 0 or 1;

R_1 represents halo, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, or hydroxy;

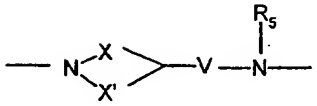
R_2, R_3 and R_4 are each H;

U is methylene;

Q is a group of formula IIa or IIc



IIa



IIc

in which V is methylene or ethylene; X is an alkylene chain containing 0 to 2 carbon atoms and X' is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in X and X' amounts to 3 or 4; and R_5 is H; and

T is pyridyl, pyrazinyl, phenyl, benzo[b]furanyl, 1,4-benzodioxanyl, or quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo; for use in reducing cravings to food or an addictive substance.

15) The use of compounds of formula I as claimed in claim 14 wherein R_1 represents methoxy, fluoro, chloro or hydroxy.

16) The use of compounds of formula I as claimed in claim 14 wherein T is 2-pyridyl, 2-pyrazinyl, phenyl, 2,3-dihydrobenzo[b]furan-7-yl, 1,4-benzodioxan-5-yl or 4-quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

17) The use of compounds of formula I as claimed in claim 14 selected from:

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrazin-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-chloropyrid-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(quinazolin-4-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine;

N-(8-Methoxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-(1-phenylpiperid-4-yl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(1,4-benzodioxan-5-yl)piperid-4-yl]methylamine;

1-[1-(1,4-Benzodioxan-2-ylmethyl)piperid-4-yl]-N-(2-methoxyphenyl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(4-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-chlorophenyl)piperid-4-yl]methylamine;

N-(5-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

1-[1-(2,3-Dihydrobenzo[b]furan-7-yl)piperid-4-yl]-N-(8-methoxy-1,4-benzodioxan-2-ylmethyl)methylamine;

N-(6-Chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(7-Chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-hydroxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

18) The use of compounds of formula I as claimed in claim 14 which are:-

(S)-(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(R)-(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride;

(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride.

19) The compound of formula I as claimed in claim 14 which is:

N-(7-Chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

20. The use of pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I, together with a pharmaceutically acceptable diluent or carrier in reducing cravings to food or an addictive substance.

21. A method of reducing cravings to food or an addictive substance which comprises the administration of a therapeutically effective amount of a compound of formula I as claimed in any of claims 1 to 19 to a patient in need thereof.

22. A method as claimed in claim 15 wherein the addictive substance is cocaine, amphetamine, nicotine, opiates, tobacco, alcohol or ecstasy.

23. The use of a compound of formula I as claimed in any of claims 1 to 19 in the manufacture of a medicament for use in reducing cravings to food or an addictive substance.